

RESEARCH CONSENT FORM

Protocol Title: Azithromycin to Prevent Bronchopulmonary Dysplasia in *Ureaplasma*-Infected Preterms: A Phase IIb Randomized, Placebo-Controlled Trial of Azithromycin to Eradicate *Ureaplasma* Respiratory Tract Infection in Preterm Infants

Study No.: HP-00054998

Principal Investigator: Rose M. Viscardi, M.D.
Contact Information (410-328-6003)

Sponsor: National Institutes of Health

You are being asked to allow your baby to participate in this research study because your baby was born early (prematurely). Your baby's participation in this study is voluntary and you may ask questions at any time. If you are consenting for someone else- a child or someone unable to provide consent themselves- then the word "you" means that person.

PURPOSE OF STUDY

Approximately 54% of babies born very early (before the 27th week of pregnancy) have a lung infection with the bacteria *Ureaplasma urealyticum*. This infection may lead to a chronic lung condition called Bronchopulmonary Dysplasia (BPD). There is no known effective treatment for this infection in preterm babies. Azithromycin is an antibiotic approved for use by the Food and Drug Administration (FDA) to treat infections caused by other bacteria in older children and adults, but has not been approved by the FDA for treating *Ureaplasma* infections in premature babies. This research study is being done as part of the FDA approval process for the use of azithromycin for this purpose. Azithromycin has been shown to be effective against *Ureaplasma* in test tube tests. By measuring blood levels of the drug in 40 preterm babies who received azithromycin as a single dose of either 10 mg or 20 mg or 3 doses of 20 mg for about every 2 pounds of body weight as part of a research study, we found that the 3 doses of 20 mg for about every 2 pounds of body weight was most effective to eliminate the *Ureaplasma* bacteria from the lungs of babies who had the infection. There were no side effects attributed to the antibiotic.

Babies with and without the *Ureaplasma* lung infection may participate in this study to evaluate azithromycin in preterm babies.

The purpose of this study is to evaluate whether 3 doses of azithromycin 20 mg/kg daily based on body weight will effectively eliminate the *Ureaplasma* bacteria from the lungs of babies who have the infection and to make sure azithromycin is safe in very preterm babies. To determine the effectiveness of azithromycin, this study will compare the active drug to a placebo. A placebo is an inactive substance made to look like an active medicine. Your child will either get the study drug, azithromycin or a placebo. Researchers use a placebo to see if the study drug works better or is safer than not taking anything. In addition, the study will find out how 3 doses of azithromycin or placebo affect markers (indicators) of inflammation in the lung in all treated babies. Finally, the study will find out how 3 doses of azithromycin or placebo affect lung health status at 6 months adjusted age (6 months plus number of weeks born early), 12 months adjusted age (12 months plus number of weeks born early) by a phone interview and lung

health and development status at 22-26 months adjusted age (22-26 months plus number of weeks born early) during a clinic visit.

A total of 140 subjects at 7 medical centers will be asked to participate in this study. Your baby will be one of approximately 40 subjects to be asked to participate at this location.

The research will be conducted at the following location(s): University of Maryland Baltimore, University of Maryland Medical System, and other sites.

PROCEDURES

This is a double-blinded study, which means that neither you or the study doctor or the study staff will know which treatment you are receiving. However, in an emergency, study doctor can get this information.

If you agree to allow your baby to participate in this study and your baby is eligible for participation you will be asked to read and sign this document. If you agree for your baby to participate, the following procedures will be performed.

1) Nose or respirator tube sample: The fluid from the baby's nose or respirator tube will be tested for the *Ureaplasma* bacteria 5 times: twice before the baby gets the study drug, once two days after the baby gets the study drug, once from 4 to 5 days after the drug, and once when the baby is 21 days old, or right before the baby is discharged, whichever comes first. These samples will be sent to the Diagnostic Mycoplasma Laboratory at the University of Alabama, Birmingham for bacterial testing. Fluid samples collected at the same times will be tested for indicators of inflammation. These samples will be obtained during routine suctioning (cleaning) of your baby's nose or the tube in your baby's windpipe that is connected to the breathing machine. You will not be contacted with the results of the bacteria tests or indicators of inflammation testing.

2) Electrocardiogram (EKG): If the baby's heartbeat is not regular on his/her bedside monitor, an electrocardiogram test (test that measures the electrical activity of the heartbeat) will be done before study drug is given. If a special pattern called prolonged QT interval is seen on the EKG, the drug will not be given. If the baby's blood potassium, magnesium, or calcium levels are low or the blood potassium level is high, the drug will not be given until the blood levels are corrected.

3) The treatment your child receives will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose what treatment your child gets. Your child will have an equal chance of being given each treatment. Neither you nor the study doctor will know which treatment you are getting. Your baby will receive either the study drug (azithromycin) or placebo (an inactive substance made to look like an active medicine) once a day for 3 days by infusion, which means that it will be given through an intravenous line (line inserted in a vein). Your baby will receive the study drug dose of 20 mg/kg based on their body weight or the same volume of placebo. Each dose will be given over a 1 hour period of time.

4) Test for BPD: If your baby is still in the hospital between 35 to 37 weeks gestation (1 month before the due date) and is still receiving extra oxygen through a tube to the nose, he/she will be tested to find out if he/she is ready to stop the extra oxygen. The extra oxygen will be decreased every 5 minutes by 2% at a time until the extra oxygen is stopped and the baby is breathing room air for 30 minutes. The decrease in oxygen will be stopped if the baby's oxygen levels are 80-89% continuously for 5 minutes or less than 80% for 15 seconds at any time. Your baby will be monitored continuously throughout the test for BPD by study staff and returned to their starting oxygen treatment as soon as the test is done.

5) Medical Records: The study doctors will review your baby's medical record. The study doctors will review the mother's medical record to make note of the treatments she received within one week of delivery.

6) **Complete questionnaires:** Before your baby leaves the hospital, a study staff member will contact you to ask questions concerning family history of lung problems such as asthma, and exposures such as smoking in the home. You will be asked to provide the name and contact information for your child's health care provider and permission to contact them after your child reaches 6 months adjusted age. Adjusted age is the age your baby would be if born on his or her due date. At 6 months adjusted age, 12 months adjusted age, and between 22 and 26 months adjusted age, a study member will contact you by phone to obtain a lung health history for your child by asking about breathing problems, illnesses, hospital stays, emergency room or doctor visits, and prescribed treatments. We will call your health care provider at this time to confirm your child's medical history.

7) **Development assessment:** When your baby is between 22 and 26 months adjusted age, the study staff will schedule a visit at the Mount Washington Pediatric Hospital Outpatient Clinic located at 1708 W. Rogers Ave., Baltimore, MD to evaluate your child's development. He/she will have a complete physical exam including a neurologic exam of his/her muscle tone, strength, and reflexes. The developmental test will evaluate your child's developmental milestones. You will receive a report about your child at the end of this visit.

Your baby will receive the same medical care whether s/he joins the study or not. In addition to the regular care for prematurity, the study doctors and nurses will follow your baby closely to make sure the infusions are safe.

If the *Ureaplasma* bacteria is obtained from the baby's nose or respirator tube culture, your child may be eligible for future studies of *Ureaplasma* bacteria as a result of his/her participation in this study. However, you may decline permission for future use of his/her samples and still agree to their participation in this study.

I _____ agree _____ do not agree to have my child's bacteria samples stored for possible use in future studies (please initial).

Please _____ do _____ do not contact me for future studies (please initial).

WHAT ARE MY RESPONSIBILITIES IF I TAKE PART IN THIS RESEARCH?

If you take part in this research, you will be responsible to:

- Ask questions about anything you do not understand
- For your child to complete all research procedures unless you formally request to withdraw from the study
- Bring your child to the follow-up clinic for scheduled visit between 22 and 26 months adjusted age
- Notify study staff of all changes to your contact information including your address, phone numbers, and e-mail address

POTENTIAL RISKS/DISCOMFORTS:

Fluid from the baby's nose or respirator tube will be collected at the time of routine suctioning by the baby's nurse. The discomfort from this procedure is minimal.

As the extra oxygen is decreased for the BPD test, the baby may experience brief periods of lower oxygen levels or brief periods of lower heart rate. The baby's oxygen level will be monitored for the entire BPD test and the extra oxygen will be adjusted if needed.

The most common side effects reported in older children and adults treated with azithromycin are gastrointestinal symptoms such as nausea, vomiting, and diarrhea (about 10%), pain at the injection site (6%), and less often vaginitis (vaginal discharge or infection), abdominal (belly) pain, loss of appetite,

rash, and itching. Fewer than 1 in 100 babies had side effects of burping, passing gas, stomach upset, mouth yeast infection (thrush), headache, sleepiness, bronchospasm (temporary narrowing of airways into the lungs), and funny taste. In most cases these symptoms were mild. Rarely, heartbeat abnormalities, allergic reactions, pseudomembranous colitis (inflammatory condition of the large intestine due to imbalance of "good" and "bad" bacteria in the intestine) and reversible hearing loss have been reported. Blood tests for liver and kidney function were out of normal range for 6% or less in older children and adults treated with azithromycin. Low numbers of white blood cells (cells that fight infection) and platelets (cells that form blood clot) have occurred in less than 1% of treated individuals. Laboratory blood tests went back to normal in other clinical trials of azithromycin. Side effects seen in infants with oral (by mouth) azithromycin and similar antibiotics include pyloric stenosis (narrowing of the stomach connection to the small intestine). Pyloric stenosis can lead to stomach blockage requiring surgery to relieve the blockage. Since azithromycin is an antibiotic, there is the risk of other bacteria that are resistant to the antibiotic starting a new illness.

There is a risk to confidentiality. This risk will be minimized by storing your baby's personal and medical information collected as part of this study in a secure location (locked file in the PI's office) and electronic data will be password protected.

There are no other additional known risks and discomforts associated with this study other than those of the infusion over and above the risks of being extremely premature and in the NICU. There may be unforeseen risks of participation in the study. If you have any questions about the risks, please ask your baby's doctor, the study doctor, or the study staff.

POTENTIAL BENEFITS

Your child may or may not benefit by taking part in this study. There is no guarantee that your child will receive direct benefit from his/her participation in this study. The benefits of participating in this study may be a chance that azithromycin may decrease inflammation in the lungs or help get rid of the *Ureaplasma* bacteria from your baby's lungs if there is an infection. Your baby's participation may provide information that may benefit other babies with *Ureaplasma* lung infection in the future by helping to determine whether 3 doses of azithromycin is effective in eliminating the infection. Still, your baby may get no direct benefit from this study. You need to decide if your child's participation in this research study is in your child's best interest.

ALTERNATIVES TO PARTICIPATION

The following alternative procedures or treatments are available if you choose not to allow your baby to participate in this study: There is no approved drug to treat *Ureaplasma* lung infections in babies now.

COSTS TO PARTICIPANTS

It will not cost you anything to take part in this study.

PAYMENT TO PARTICIPANTS

You will receive a \$50 gift card after the completion of your child's neurodevelopmental assessment and lung health questionnaires at the end of the study when your child is 22-26 months adjusted age.

CONFIDENTIALITY AND ACCESS TO RECORDS

All of the baby's samples will be coded with a study number rather than their name or other identifier. We will keep your name and contact information on file to contact you at 6 months adjusted age, 12 months adjusted age and between 22 to 26 months adjusted age and in case we need to notify you of any important information about the study. Only the principal investigator, Dr Rose Viscardi and her staff will have access to your baby's private information. The data from the study may be published. However, you will not be identified by name.

Efforts will be made to limit your personal information, including research study and medical records, to people who have a need to review this information. People designated from the institutions where the study is being conducted and people from the sponsor will be allowed to inspect sections of your medical and research records related to the study. Everyone using study information will work to keep your personal information confidential. Your personal information will not be given out unless required by law. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this organization, the Food and Drug Administration, Department of Health and Human Services, and National Institutes of Health. The monitors, auditors, the IRB, and the Food and Drug Administration will be granted direct access to your medical records for verification of the research procedures and date. By signing this document you are authorizing this access.

A description of this clinical trial is available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

RIGHT TO WITHDRAW

Your participation in this study is voluntary. You do not have to take part in this research. You are free to withdraw your consent at anytime. You will be told of any significant new findings which develop during the study which may affect your willingness to participate in the study. There are no adverse consequences (physical, social, economic, legal, or psychological) if you decide to withdraw from the research. Refusal to take part or to stop taking part in the study will involve no penalty or loss of benefits to which you are otherwise entitled. If you are an employee or student, your employment status or academic standing at UMB will not be affected by your participation or non-participation in this study. If you decide to stop taking part, or if you have questions, concerns, or complaints, or if you need to report a medical injury related to the research, please contact the investigator Dr. Rose Viscardi at 410-706-1913 during the day and at 410-328-6003 after hours. If you withdraw from this study, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

CAN I BE REMOVED FROM THE RESEARCH?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include a treatment becomes available for him/her that may be better for him/her than the care available in the study, or he/she has a serious reaction during the study. The Food and Drug Administration or the sponsor can also end the research study early. The study doctor will tell you about this and you will have the chance to ask questions if this were to happen.

UNIVERSITY STATEMENT CONCERNING RESEARCH RISKS

The University of Maryland, Baltimore (UMB) is committed to providing participants in its research the rights due them under State and federal law. You give up none of your legal rights by signing this consent form or by participating in the research project. This research has been reviewed and approved by the Institutional Review Board (IRB). Please call the Institutional Review Board (IRB) if you have questions about your rights as a research subject.

Participating in research may result in an injury, as explained above. If you suffer an injury directly related to your participation in this project, UMB and/or one of its affiliated institutions or health care groups will help you obtain medical treatment for the specific injury and provide referrals to other health care facilities, as appropriate. UMB and/or its affiliated institutions or health care groups will not provide you with financial compensation or reimbursement for the cost of care provided to treat a research-related injury or for other expenses arising from a research-related injury. The institution or group providing medical treatment will charge your insurance carrier, you, or any other party responsible for your treatment costs. If you incur uninsured medical costs, they are your responsibility. The HRPO will assist

you in contacting the sponsor if you have an injury caused by the sponsor's drug or device under study. Uninsured medical costs to treat research related injuries not caused by the drug or device under study are your responsibility. The study staff can give you more information about this if you have a study injury.

By signing this Consent Form, you are not giving up any legal rights. If this research project is conducted in a negligent manner and you are injured as a direct result, you may be able to recover the costs of care and other damages from the individuals or organizations responsible for your injury.

If you have questions, concerns, complaints, or believe you have been harmed through participation in this research study as a result of researcher negligence, you can contact members of the IRB or the Human Research Protections Office (HRPO) to ask questions, discuss problems or concerns, obtain information, or offer input about your rights as a research participant. The contact information for the IRB and the HRPO is:

University of Maryland School of Medicine
Human Research Protections Office
620 W. Lexington Street, Second Floor
Baltimore, MD 21201
410-706-5037

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

If you agree to participate in this study, please sign your name below.

<p>_____ Participant's Signature</p> <p>Date: _____</p> <p>_____ Investigator or Designee Obtaining Consent Signature</p> <p>Date: _____</p> <p>Time: _____</p>	<p>_____ Signature of Parent/Guardian <i>(When applicable)</i></p> <p>Relationship: _____</p> <p>Date: _____</p> <p>_____ Witness*</p> <p>Date: _____</p>
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